## REMARKS

The Specification has been amended to correct minor informalities. Claims 18, 19, 21, and 23-33 have been amended and new claims 38-45 have been added. The changes made to the Specification and Claims by the current amendment, including ~~deletions~~ and additions, are shown herein with deletions designated with a strikethrough and additions underlined. No new matter has been added herewith. Support for the amendment to Claims 18, 19, 21, 23, 29, and 30 and new claims 38-45 can be found in the Specification and claims as filed, for example for the Claim 18 amendments and new claim 39 on page 14, paragraph 42; the explanation for N15-Bcl-2 in the amendments to Claim 19 and new claims 41, 42, and 44 can be found on page 64, paragraph 188; the amendments to Claims 21, 23, 29, and 30 can be found on page 33, paragraph 105 which includes one exemplary apoptosis assay.

**Election**

The Examiner has further restricted the claims to withdraw Claims 20 and 22, because they are dependent upon Claim 17 and are properly grouped with the non-elected invention of Group V.

**Rejection under 35 U.S.C.§112, first paragraph**

The Examiner has rejected Claims 24-26 and 30 as not complying with the written description requirement. More specifically, the Examiner rejected Claims 24-26 as drawn to functional derivatives and natural variants of TR3 which the Examiner believes are not adequately described in the specification. However, the claims have been amended to include the functional language: "wherein said Bcl-2 binding compound binds to Bcl-2 and modulates the activity of Bcl-2 in a cell so as to be inductive of apoptosis" (Please see Claim 1 for support for the added language). The amended claims therefore require that the polypeptide possess a specific biological activity, i.e.; the ability to bind to Bcl-2 and modulate its activity so as to induce apoptosis. There is no substantial variability within the species which fall within the scope of the claim. Further, the structure of the fragment in claims 25 and 26 are disclosed in the Specification, for example at page X, paragraph X.

The Examiner has rejected Claim 30 as drawn to functional derivatives/natural variants of TCTP. Again, the claim has been amended to include the functional language: "wherein said

Bcl-$X_L$ binding compound binds to Bcl-XL and modulates the activity of Bcl-XL in a cell so as to be inductive of apoptosis".

There is extensive support in the specification as filed for functional derivatives and natural variants which are inductive of apoptosis, including: Example 3 which provides methods of testing the compounds for the function, Example 7 and other parts of the specification which provide mutants which remove all or part of the DNA-binding domain (residues 168-467) and fragments which include the DC1 region of TR3; Examples 6, 7, 8, and 9 which provide methods for screening peptides, and structural-based drug design; all of which can be used to identify functional derivatives and natural variants. Thus, Applicants respectfully request withdrawal of the rejection under 35 U.S.C.§112, first paragraph.

**Rejection under 35 U.S.C.§112, second paragraph**

Claims 19, 21, 24-27, 30 and 33 have been rejected as being indefinite for not spelling out the following: TCTP, TR3, NMR, BH3, SAR, and DC1. Applicants have amended the claims to define each term. However, since DC1, BH3 and TR3 are not direct acronyms they should not be required to be "spelled out" and are believed definite as written.

Claims 19 and 21 are believed indefinite because the phrases "N15-Bcl-2" and "N15-Bcl-XL" are not explained sufficiently in the claims or specification. However, $N^{15}$ is a labeled isotope corresponding to Nitrogen 15, used very similarly to C13 in NMR (see page 64, paragraph 188). One of skill in the art would know that this isotope is commonly used and would know that this is what "N15-Bcl-2" and "N15-Bcl-XL" refer to. To clarify, however, the claims have been amended to show the "15" in superscript. Thus, Applicants respectfully request withdrawal of the indefiniteness rejection.

Claims 24-28 are believed indefinite for being dependent without further clarifying the independent claim they depend from. Claims 24-27 have been amended to be dependent upon Claim 23. The claims have been amended to further limit the independent claim from which each depends.

Claims 19, 21, and 28 are believed indefinite for using NMR but not explaining the steps involved in the process. Claims 19 and 21 have been amended to remove any reference to NMR. It appears that the Examiner meant to refer to Claim 27 because Claim 28 does not mention

NMR. Claim 27 has been amended to clarify that NMR is used to identify the relationship between Bcl-2 and the candidate agent.

Claims 24-28 are believed indefinite for not having sufficient antecedent basis for the limitation "Bcl-2" in line 1. The claims have been amended to depend from Claim 23, which provides antecedent basis.

**Rejection under 35 U.S.C.§102(b)**

The Examiner has rejected Claims 18 and 31 as anticipated by Li et al. (2001) Journal of Biological Chemistry, Vol. 276, No. 50, pp 47542-47549.

> To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. ...There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

Li et al. provides an apoptotic protein (which they call "fortilin") which was identified through a two-hybrid library screening using Bcl-2. After screening, the compound identified was assayed using immunohistochemistry to detect the affinity for binding to Bcl-2. The compound was further assayed as to apoptotic ability (see the bottom of page 47546 and the top of page 47547).

Claims 18 is drawn to: a method of identifying molecules that induce apoptosis by determining the ability of the molecule to bind to a Bcl-2-family protein in the loop region and modulate the activity of said protein so as to be inductive of apoptosis. Claim 31 includes the presence of a multidomain Bcl-2 family protein.

With respect to Claim 18, Li does not anticipate identifying a molecule which binds to the loop region of Bcl-2 or a family member, because the importance of the loop region was not recognized in the prior art. Li et al. does not anticipate the claimed invention because Li et al. does not teach all of the claim elements.

With respect to Claim 31, there is no language in Li et al. to suggest that the two hybrid system included in addition to Bcl-2, a multidomain Bcl-2 family protein, thus, Li et al. is not anticipatory because Li et al does not teach all of the claimed elements.

**Rejection under 35 U.S.C.§102(b)**

The Examiner has rejected Claims 21, 24-30, and 32 as anticipated by Petros et al. (2000) Protein Science, vol. 9, pp 2528-2534.

Petros, et al. teach a method of identifying compounds that bind with a high affinity to Bcl-XL using nuclear magnetic resonance (NMR). Fluorescence spectroscopy identified the binding affinity by identifying dissociation of a fluoresceinated peptide from Bcl-XL. There is no step for assaying the ability of the compound to induce apoptosis in Petros, et al., nor is there any suggestion in this reference that the compounds identified would induce apoptosis. This function is unrecognized in the cited reference.

Claim 21 is directed to a method which employs isotope-labeled Bcl-XL to identify compounds which bind to Bcl-XL. As amended, the method also includes the step of "assaying the compound to determine whether it induces apoptosis." Thus, Petros et al. do not teach all of the claimed elements. The cited reference does not include a step of assaying the compound to identify whether it induces apoptosis.

Claims 23 and 29 are directed to a method for identifying agents that induce apoptosis by detecting a binding compound which induces a conformational change, contacting the complex with a candidate agent and identifying whether the binding compound dissociates, and assaying the candidate agent to determine whether the agent induces apoptosis. There is nothing in Petros et al to suggest that the candidate agent would induce apoptosis, such that it should be assayed for its ability to induce apoptosis. Thus, Petros et al. do not anticipate the claimed invention.

**Conclusion**

Should there be any question in relation to the above-identified patent application, the Examiner is respectfully requested to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: 3/4/2005

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